

TRIPLET PREGNANCY COMPLICATED WITH ONE HYDATIDIFORM MOLE AND PREECLAMPSIA IN A 46,XY FEMALE WITH GONADAL DYSGENESIS

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SUMMARY

Objective: We present a case of triplet pregnancy with a complete hydatidiform mole, a condition carrying a significant risk to both mother and fetuses and, therefore, raising an important issue on prenatal care.

Case Report: A 36-year-old patient with gonadal dysgenesis and a 46,XY karyotype successfully conceived a triplet pregnancy after oocyte donation and *in vitro* fertilization. At mid-trimester, the pregnancy was seen harboring a hydatidiform mole along with two other fetuses by ultrasound. Fetal karyotyping of both fetuses revealed normal results. Serum human chorionic gonadotropin levels were followed up throughout the remainder of pregnancy. At 33 weeks of gestation, preeclampsia ensued with worsening of maternal renal function and high blood pressure, so cesarean section was arranged to deliver a set of two surviving twins. Prophylactic bilateral gonadectomy was done at the same time to curtail the possibility of future malignancy development. Upon pathologic examination of the placenta, hydropic chorionic villi with central cistern formation and nonpolar trophoblastic hyperplasia with atypia and necrosis were found, compatible with complete hydatidiform mole. The gonads showed streaks of fibrous tissue, which resembled ovarian stroma and hilus cells, and an unremarkable tube. Maternal serum human chorionic gonadotropin levels declined gradually to normal level at two months after delivery.

Conclusion: This is the first report of triplet pregnancy complicated with one complete hydatidiform mole and preeclampsia in a 46,XY female with gonadal dysgenesis. Our case demonstrated that prolonged gestation with both surviving fetuses was possible by applying intensive monitoring of the whole pregnancy. [*Taiwan J Obstet Gynecol* 2007;46(3):276-280]

Key Words: gonadal dysgenesis, hydatidiform mole, preeclampsia, triplet pregnancy

Introduction

Triplet pregnancy with a complete hydatidiform mole is a rare condition that has only been reported in a handful of cases [1-12]. All of them happened in genetic female patients, and only three of these pregnancies resulted in live fetuses [8,11,12]. Herein, we present a case of a 46,XY female with gonadal dysgenesis who conceived a triplet pregnancy with one complete

hydatidiform mole after oocyte donation and *in vitro* fertilization. With expectant management including serial measurement of β -hCG, despite a later complication of preeclampsia, delivery of two surviving fetuses was achieved.

Case Report

A 36-year-old Taiwanese was diagnosed with ovarian failure at the age of 16. Initially, she went to a local hospital in 1986 because of primary amenorrhea and lack of development of secondary sexual characteristics (both breast development and pubic hair development at Tanner stage I). Nevertheless, she had a normal uterus,

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but the follicle stimulating hormone level was high (61 mIU/mL). Under the impression of ovarian failure, she was given sequential estrogen and progesterone, which later resulted in regular menses.

She got married at age 35 and underwent *in vitro* fertilization and embryo transfer in the same year using donor oocytes at a local hospital. Then, she became pregnant with triplets (two fetuses and one suspected mole). Karyotyping of two fetuses revealed a normal 46,XY and 46,XX. At the same time, the patient's chromosome was checked, which revealed 46,XY. Polymerase chain reaction study with primers (forward 5'-TACAT-GTTATGTGCTATGCC-3'; backward 5'-CACATTATAT-AATATGTATGTTGTC-3') [13] confirmed the presence of testicular determining sequence, SRY.



Figure 1. Ultrasound at 20 weeks of gestation revealed two live fetuses and one hydatidiform mole (arrowhead) that was located at the posterior uterine wall with grape-like appearance.

At 20 weeks of gestation, she was referred to our institute for further prenatal care. Ultrasound revealed two fetuses and another honeycomb-like mass, 10.73×3.88 cm in size, at the posterior wall (Figure 1) with rich vascularity, suggestive of molar tissue. A series of quantitative measurements of serum β -hCG level followed, which revealed a level of 163,090 mIU/mL at 20 weeks, rose to 196,980 mIU/mL at 21 weeks and then plateaued at 80,520 mIU/mL at 30 weeks (Figure 2). Serial sonography documented normal anatomy and appropriate growth of both fetuses; the molar tissue remained stationary in size and echogenicity throughout the pregnancy. During pregnancy, gestational hypertension (160/93 mmHg) developed at 28 weeks of gestation, and oral medication with methyldopa was prescribed. Proteinuria (500 mg/dL) occurred at 33 weeks of gestation, completing a diagnosis of preeclampsia. Owing to worsening of renal function with elevated blood urea nitrogen and creatinine, hyperkalemia, and poor blood pressure control, cesarean section was performed after a complete course of corticosteroid to boost fetal lung maturity. Two live babies with good Apgar scores were born, weighing 1,800 g and 1,860 g. Both neonates had uneventful perinatal outcome and were discharged in good condition. The placenta weighed 850 g with part of it containing grape-like tissue that was consistent with molar change (Figure 3). Prophylactic gonadectomy was performed at the same time during cesarean section. Microscopically, the molar tissue revealed large and hydropic chorionic villi with central cistern formation and nonpolar trophoblastic hyperplasia with atypia

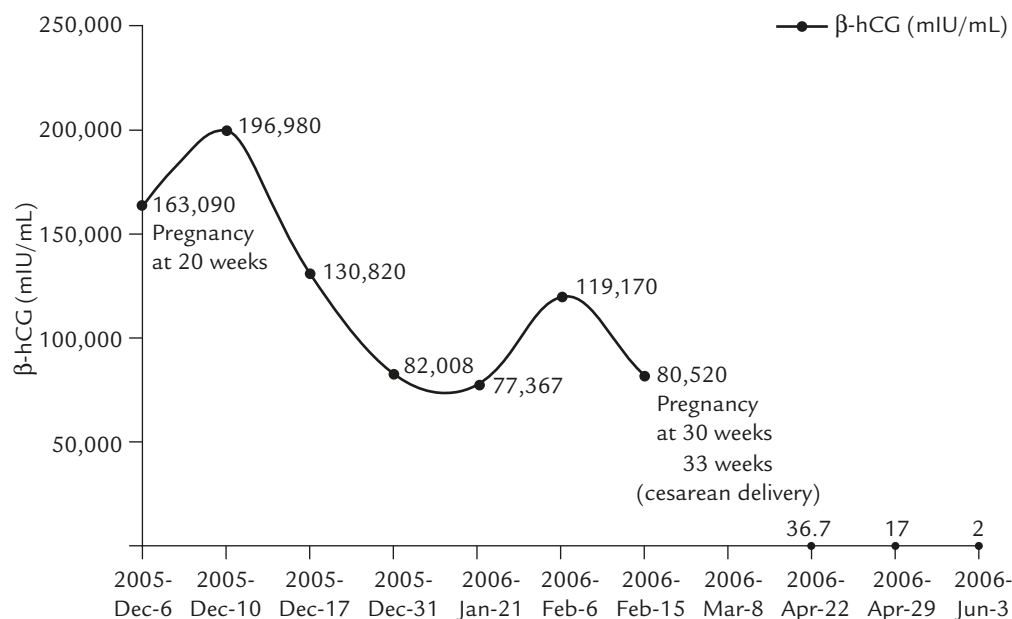


Figure 2. Serial β -hCG change during pregnancy and postcesarean delivery in a triplet pregnancy with coexistence of one hydatidiform mole.

and necrosis, which were compatible with complete hydatidiform mole. The pathology of the gonads showed streaks of fibrous tissue, which resembled ovarian stroma and hilus cells, and an unremarkable

tube. Maternal serum human chorionic gonadotropin levels declined gradually to normal level at two months after delivery.



Figure 3. Gross appearance of part of the placenta where grape-like tissue was found, indicating a mole (arrow).

Discussion

The incidence of coexisting mole and live fetus is estimated to complicate 1 in 22,000 to 1 in 100,000 pregnancies [14], which may occur spontaneously or as a consequence of assisted reproductive technology. The incidence of a twin pregnancy with complete hydatidiform mole and a coexisting fetus after *in vitro* fertilization and embryo transfer (IVF-ET) is not greater than that of the general population [15]. Triplet pregnancy with coexistence of complete hydatidiform mole is a rarer condition, which has been reported previously in 12 cases (as summarized in the Table). To our knowledge, our case is the first report of triplet pregnancy with coexistence of complete hydatidiform mole happening

Table. Cases of triplet pregnancy consisting of a complete hydatidiform mole and two fetuses: maternal and fetal outcomes

Case	Hormone therapy	Gestational age at delivery (wk)	Number of surviving fetuses	Maternal complications	Maternal chromosome
Sauerbrei et al [3]	Clomiphene	22	0	Vaginal bleeding, preeclampsia at 22 weeks	46,XX
Ohmichi et al [4]	hMG + hCG	17	0	Vaginal bleeding, persistent trophoblastic tumor	46,XX
Azuma et al [5]	hMG + hCG	19	0	Vaginal bleeding	46,XX
van de Geijn et al [6]	GIFT	24	0	Vaginal bleeding	46,XX
Shahabi et al [7]	Clomiphene	17	0	Persistent trophoblastic tumor, choriocarcinoma, lung metastasis, hyperthyroidism	46,XX
Shozu et al [8]	IVF-ET	15	0	Vaginal bleeding, persistent trophoblastic tumor	46,XX
Higashino et al [9]	Clomiphene + FSH + hCG	15	0	Preeclampsia, secondary hyperthyroidism, persistent trophoblastic tumor	46,XX
Amr et al [10]	Clomiphene + hCG	30	1	None	46,XX
Rajesh et al [11]	None	24	0	Vaginal bleeding	46,XX
Malhotra et al [12]	None	21	0	Vaginal bleeding	46,XX
Takagi et al [14]	hMG + hCG	28	2	Persistent trophoblastic tumor, lung metastasis	46,XX
Bovicelli et al [15]	IVF-ET	31	1	None	46,XX
Present case	IVF-ET	33	2	Preeclampsia	46,XY

hMG = human menopausal gonadotropin; hCG = human chorionic gonadotropin; GIFT = gamete intrafallopian transfer; IVF-ET = *in vitro* fertilization and embryo transfer.

in a 46,XY female with gonadal dysgenesis. Concerning fetal outcomes, it seems that fetal survival until term is unlikely because of the maternal complications of the mole itself. Among the cases, miscarriages occurred in nine of them, two pregnancies ended up with one surviving fetus, and there was only one pregnancy resulting in survival of both fetuses. In our case, the outcome was excellent compared with other cases reported previously. Our case is the second report of survival in both fetuses.

Hydatidiform molar change is the pathologic manifestation of genetically abnormal conceptions, in which an excess of paternally derived genetic material results in abnormal fetoplacental development and placental villous trophoblast hyperplasia. Pregnancies in which molar change has been reported in association with a live fetus generally represent dizygotic twin pregnancies; on the other hand, partial hydatidiform molar tissue usually results from triploidy. In cases of dizygotic twin pregnancies, there is usually clear distinction, both sonographically and pathologically, between the molar and non-molar placenta. It has been reported that coexistence of hydatidiform molar and excessive placental growth is associated with an increased risk of preeclampsia, vaginal bleeding, hyperemesis gravidarum, hyperthyroidism, premature delivery, and persistent gestational trophoblastic disease [16]. Although a complete hydatidiform mole incurs a higher risk of invasive trophoblastic disease to the mother, it offers a chance of delivering a healthy newborn infant. In contrast, partial mole is lethal for the fetus and carries a small risk of a persistent trophoblastic tumor to the mother.

A recent review of 126 cases of twin pregnancies and coexisting complete hydatidiform mole from Charing Cross Hospital has shown a live birth rate of 25%, a 20% risk of persistent gestational trophoblastic disease, and a 75% rate of pregnancy loss, including spontaneous miscarriages, stillbirths and therapeutic termination [17]. But with triplet pregnancy and coexisting mole, our review saw a total of 13 cases (including our case), most of which carrying significant risks to both mother and fetuses. The fetal loss rate of both fetuses was 69.2% (9/13), while maternal complications of vaginal bleeding occurred in 53.9% (7/13), persistent trophoblastic tumor in 38.5% (5/13), preeclampsia in 23% (3/13) and secondary hyperthyroidism in 15.4% (2/13) of cases. Compared with the previous report, the risk of persistent gestational trophoblastic disease in triplet pregnancy with coexisting complete hydatidiform mole is nearly two times that in twin pregnancy with coexisting mole (38.5% vs. 20%).

Preeclampsia that is associated with hydatidiform mole is considered to be clinically aggressive, so the

presence of the condition should be an indication for imminent delivery. Other indications for termination of the pregnancy include the development of intractable vaginal bleeding, severe hyperemesis gravidarum, hyperthyroidism, or evidence of trophoblastic embolization. In our case, the risk factors for development of preeclampsia were nulliparity, age older than 35 years, multifetal gestation, and hydatidiform mole; the delivery took place at 33 weeks of gestation. The trend toward a lower frequency of preeclampsia in the pregnancy resulting in surviving infants may suggest more benign trophoblast lesions in this group of patients. On the other hand, higher pre-evacuation β -hCG levels had a greater propensity to develop persistent gestational trophoblastic tumor. So, it is important to follow up on such cases with serial β -hCG and sonography, not only during pregnancy but also after delivery, in order to spot early signs of progression or even metastasis.

Pure gonadal dysgenesis, also known as Swyer syndrome, is a sex-reversal disorder resulting from embryonic testicular regression sequences, especially during the first few weeks of fetal life, and may be induced by mutations in the SRY gene. The Y chromosomal SRY gene (sex-determining region of Y), which has been mapped to a region 5 kb proximal to the pseudoautosomal boundary on the short arm of the Y chromosome, is required for regular male sex determination. SRY expression initiates a network of gene activity that transforms the undifferentiated gonad (i.e. genital ridge) into a testis, so mutations in SRY gene result in XY sex reversal and pure gonadal dysgenesis. Other than mutations in the SRY gene, mutations in the SRY regulatory elements or other genes involved in the sex differentiation pathway can also lead to gonadal dysgenesis [18]. Although the SRY gene was tested positive in our case, it apparently had one malfunction that led to development of internal female genital organs (uterus and fallopian tubes) without release of the müllerian inhibition factor. Patients with both gonadal dysgenesis and Y-chromosome presence are at high risk of developing gonadal tumors (gonadoblastoma and dysgerminoma), and therefore, prophylactic removal of the gonads is advised to preclude future malignant change. So, we performed concomitant prophylactic gonadectomy for our patient during cesarean delivery, and fortunately, both gonads were free of malignancy then. The patient was placed on hormonal therapy to induce regular menstrual cycles in the postpartum period.

In summary, this is the first report of triplet pregnancy complicated with one complete hydatidiform mole in a 46,XY female with gonadal dysgenesis. With expectant management, the pregnancy was prolonged for as long as 33 weeks of gestation so that both

fetuses could have a good chance of survival. Although preeclampsia is rarely reported in a pregnancy by a 46,XY female, its management, however, is not different from that for a normal female. Triplet pregnancy with coexistence of complete hydatidiform mole carries significant risks to both mother and fetuses. During the pregnancy, fetal karyotyping and serial serum β -hCG follow-up is important. In addition, prophylactic gonadectomy and keeping a close watch for signs of progression or metastatic gestational trophoblastic disease after delivery are mandatory.

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